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PATENT SPECIFICATION

NO DRAWINGS

1,017,674

Date of Application and filing Complete Specification: Sept. 4, 1964.
No. 36293/64.
Application made in Switzerland (No. 11155) on Sept. 10, 1963.
Complete Specification Published: Jan. 19, 1966.

1,017,674

Index at acceptance:—A5 B(3, 4, 6)
Int. Cl.:—A 61 k 3/78

COMPLETE SPECIFICATION

Coated Pharmaceutical Compositions

We, F. HOFFMANN-LA ROCHE & Co., Aktiengesellschaft, a Swiss Company of 124—184 Grenzacherstrasse, Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to novel coated pharmaceutical compositions. More particularly, the invention is concerned with pharmaceutical compositions the active medicament of which is neither released in the stomach nor in the earlier part of the small intestine but in the later part of the small intestine and in the colon, and with the preparation thereof.

Cases occur where it is undesirable for a medicament to be released into the stomach from the granulate, tablet, gelatin capsule or dragée in which it is embodied. This applies, for example in cases where the medicament is decomposed in the stomach by the hydrochloric acid and/or the enzymes of the gastric juices. It also applies where the particular medicament used irritates the gastric mucosa. To avoid premature release of the active medicament it has been the practice to coat the granulate, tablet, gelatin capsule or dragée which contains the medicament, with a material which is neither attacked nor dissolved nor digested by the gastric juices. One type of suitable coating is a lacquer which resists the action of the gastric acid; that is to say, hydrochloric acid. Such coatings, however, are not normally resistant to the alkaline digestion juices of the duodenum and of the upper part of the small intestine, and as a result, the coated composition is dissolved or decomposed prematurely—with the ensuing unwanted liberation of the medicament.

It is also known that pharmaceutical preparations can be coated with waxes and fats and that the resulting compositions will be resistant to attack by the gastric acid. However, fat and wax coated products are only slowly decomposed by the alkali in the intestinal juice and occasionally not completely unless the decomposition is facilitated by the action of the intestinal and pancreatic enzymes (particularly lipase) and the wetting and emulsifying action of the bile.

None of the prior measures described in the foregoing paragraphs are really capable of preventing the liberation of the active medicament in the duodenum and the upper sections of the small intestine while yet permitting its liberation when the pharmaceutical composition has reached the lower sections of the small intestine or even the colon. Thus, if the active medicament is of such nature that it causes irritation in the stomach, duodenum or jejunum, and/or causes undesirable side effects (for example, abdominal pains or emesis) the measures described heretofore are completely ineffective in avoiding this irritation or the side effects. Not only are they ineffective on this account but, relatively more important, they are medically ineffective where the nature of the ailment to be treated is such that the medicament must be liberated only in the ileum or colon where its action is to be exerted.

The reasons why the active drug is released before it reaches the ileum when the procedures of the prior art are utilized is because the lacquer coating, while resistant to acidic gastric juices, dissolves as soon as the content of the intestine becomes alkaline, and the fat or wax coating is digested when it comes into contact with the enzymes of the duodenum.

It will be appreciated that many other factors, including physiological differences which are encountered in the gastro-intestinal tracts of particular patients, have a distinct bearing on the efficacy of coatings for medicaments. For example, it is not uncommon that, due to a decrease in acid secretion or a reverse flow of the alkaline duodenal juice, the gastric juices become only slightly acid to neutral in reaction or even alkaline. Since those lacquer

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ERRATA

SPECIFICATION No. 1,017,674
Amendment No. 1

Page 2, line 56, *for* "aplied" *read* "applied"
Page 3, line 123, *for* "diethylamine" *read* "diethylamino"

THE PATENT OFFICE
16th March 1966

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medicament to be released into the stomach from the granulate, tablet, gelatin capsule or dragée in which it is embodied. This applies, for example in cases where the medicament is decomposed in the stomach by the hydrochloric acid and/or the enzymes of the gastric juices. It also applies where the particular medicament used irritates the gastric mucosa. To avoid premature release of the active medicament it has been the practice to coat the granulate, tablet, gelatin capsule or dragée which contains the medicament, with a material which is neither attacked nor dissolved nor digested by the gastric juices. One type of suitable coating is a lacquer which resists the action of the gastric acid; that is to say, hydrochloric acid. Such coatings, however, are not normally resistant to the alkaline digestion juices of the duodenum and of the upper part of the small intestine, and as a result, the coated composition is dissolved or decomposed prematurely—with the ensuing unwanted liberation of the medicament.

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films which are normally resistant to gastric juices, start to swell and dissolve at a pH of about 4 or higher, there is a distinct possibility that because of the physiological conditions mentioned heretofore, a lacquer coated medicament will be released while still in the stomach. On the other hand, it is well known that fat and wax coatings are more durable than lacquer coatings since they are, to a great extent, not influenced by the pH of the system. However, such coatings are not completely satisfactory since, frequently, they are damaged by the peristalsis of the stomach causing them to release their contents. This is especially true in those cases in which the fat or wax that is used contains components which melt wholly or partly at a temperature of up to about 37°C. Finally, it is well known that the application of fat or wax coatings to pharmaceutical compounds, leaves much to be desired from a technical standpoint. Even under the most favourable conditions it is difficult to obtain a completely satisfactory product.

In general, polyelectrolytes which have carboxyl groups in their structure are representative of substances which are resistant to gastric juices. Furthermore, such polyelectroylytes are insoluble in acid and non-resistant to intestinal juices. On the other hand, polyelectrolytes having a number of basic amino groups constitute substances which are acid-soluble, non-resistant to gastric juices and, more significantly, resistant to intestinal juices. It has now been found in accordance with this invention that by using such substances in proper sequence one can obtain a coated pharmaceutical composition from which the release of the active medicament can be effectively controlled or regulated.

Accordingly, the pharmaceutical compositions of the present invention are characterized in that they comprise: (1) a nucleus (for example, a tablet, granulate, granule or gelatine capsule) containing the active drug and conventional pharmaceutical adjuvants, coated in sequence with (2) a layer of an acid-soluble coating material which is resistant both to alkalis and intestinal juices, (3) a water-soluble intermediate layer of a type to be described hereinafter and (4) a layer of an alkali-soluble coating material which is resistant to acid and to gastric juices.

The first layer, that is the acid-soluble material which is resistant to alkalis and to intestinal juices, can be aplied if desired directly to the nucleus. Alternatively, the nucleus can be coated first with a hydrophilic or insulating layer which may consist of sugar syrups (with or without mucilages) or solutions of solid polyethyleneglycols and, thereafter, with the acid-soluble material. After the application of the acid-soluble layer is complete, the coated nucleus is coated with an additional insulating intermediate layer of the type described heretofore. Subsequently, there is applied to the thus coated nucleus a solution of a substance which is resistant to gastric juices. If desired, there can be applied to the coated product thus obtained an external sealing layer comprising a solution containing the previously mentioned hydrophilic substances. Optionally, colouring materials can be incorporated into the product as an adjuvant in such layer. Finally, the coated compositions can be provided with a commercially attractive appearance by means of conventional glazing and polishing methods and techniques.

The manner in which the coating compositions of this invention function to provide the desired release of the active medicament is briefly as follows: The coated pharmaceutical composition passes into the stomach where it is subjected to the action of the normally acid gastric juices. The external hydrophilic layer, if present, dissolves. However, the coating layer comprising the material which is resistant to the stomach juices is not dissolved therein. Accordingly, the composition remains intact so long as it is maintained in the acid environment. However, when the medium becomes only weakly acid or neutral or slightly alkaline (as happens when the composition passes along the gastro-intestinal tract) the acid resistant layer swells and ultimately dissolves. Subsequently, the intermediate insulating layer (comprising the hydrophilic materials named heretofore) also dissolves. The next layer, that is the layer comprising the substance which is acid soluble and resistant to intestinal juices, remains intact since the system is no longer acid after passing from the stomach into the gastro-intestinal tract. The layer, accordingly, does not dissolve and the preparation does not disintegrate. It has been found, however, that, under such circumstances, an active medicament is relatively speaking, very slowly released from the composition if it is a water-soluble material. This is brought about because the layers which coat the drug are not completely impermeable; rather, the layers are porous and, to some extent, may be considered to be semi-permeable membrane enveloping the medicament. According to particular needs and requirements, the porosity of the layers can be increased or decreased to regulate the release of the drug. For example, the porosity of the coating layers can be reduced by the use of solid materials, such as talc, pigments, calcium stearate and magnesium stearate in the coating composition. The use of larger quantities of coating material does not eliminate the porosity. However, by varying the amounts of coating solutions employed one can change the size of the pores so that the rate at which the drug is diffused from the product can be regulated.

The coatings which are provided by the practice of the present invention are such that even when the gastric juices are weakly acid

or neutral or when the stomach contents are alkaline the active medicament is protected from premature release. Under such circumstances the external layer, that is the layer comprising the material which is resistant to gastric juices but not resistant to alkali, is dissolved. The stomach liquids, after the intermediate insulating layer has been dissolved, reach the layer comprising the material which is resistant to intestinal juices and alkali. This layer is not, however, dissolved or disintegrated. The diffusion of the active medicament (mentioned heretofore) does, however, begin at this point. By appropriate means, for example by suitable alteration in the coating formulation and/or the quantity of the coating applied, one can regulate the rate at which the active drug or medicament is diffused from the composition. By this means, provision may be made to ensure that the active medicament will for the most part be released only after it has reached the ileum.

It has been found also that the diffusion of the active component of the composition through the alkali-resistant layer can be regulated by incorporating into the nucleus to be coated water-insoluble and/or alkali-insoluble materials as well as slowly digestible or even non-digestible inert substances such as barium sulphate, tricalcium phosphate, calcium carbonate, high-melting waxes, zein or hydrogenated castor oil.

It will be immediately apparent that the present invention is not restricted to compositions coated only once with an alkali - soluble material and once with an acid - soluble material. By means of an intermediate hydrophilic insulating layer of the type already described between successive layers it is possible to apply to the medicament-containing nucleus multiple layers of either one or both types of alkali-soluble and acid-soluble materials. For example, there may be applied to the nucleus first a coat of material which is resistant to intestinal juices followed in sequence by an intermediate hydrophilic layer, a second coat of the material resistant to intestinal juices and an additional intermediate hydrophilic layer, and then a layer which is resistant to gastric juices followed by an external sealing layer. On the other hand, there can be applied to the nucleus a layer which is resistant to intestinal juices followed in succession by an intermediate layer of a hydrophilic substance, a coat of material which is resistant to gastric juices, an intermediate layer of a hydrophilic substance, a second coat of a material which is resistant to gastric juices followed by the external sealer coat. Furthermore, there can be applied to the nucleus two layers of a material which is resistant to intestinal juices (such layers being separated by an intermediate layer of a hydrophilic substance), a second intermediate hydrophilic insulating layer followed by two layers of a material which is resistant to gastric juices (such layers of material being separated by an intermediate hydrophilic insulating layer) followed by the external sealer coat. The foregoing is included herein merely for the purpose of illustration, it having been established that up to three layers of material which is resistant to gastric juices and/or up to three layers of material which is resistant to intestinal juices can be applied. Additionally, there may be distributed throughout the insulating layers, if desired, portions of the same medicament which is present in the nucleus. On the other hand, there may be incorporated into the intermediate hydrophilic layers one or more medicaments which are different from that present in the nucleus.

In the practice of this invention, there may be used to provide the coating resistant to gastric juices a film-forming polyelectrolyte containing carboxyl groups. Examples of such materials are: natural lacquers (such as keratin and shellac), cellulose esters containing carboxyl groups (such as acetyl-phthalyl cellulose, acetyl - succinyl cellulose), carboxyl - containing co-polymers containing maleic acid or maleic anhydride as the acidic component (such as co-polymers of styrene and maleic anhydride, co-polymers of the butyl partial ester of maleic acid with styrene and small quantities of acrylic acid, co-polymers of maleic anhydride and vinyl methyl ether) and carboxyl-containing co-polymers with acrylic acid or methacrylic acid as acidic component (such as co-polymers of styrene and methacrylic acid).

To provide a coating which is resistant to intestinal juices, there is used in the practice of this invention a film-forming basic amino-containing polyelectrolyte. Examples of such materials are: amino - containing polyacrylates or polymethacrylates (e.g. polymers or mixtures of polymers of aminoalkyl esters of acrylic acid or methacrylic acid, such as the dimethyl-amino - ethyl ester of acrylic acid or methacrylic acid), amino - containing polysaccharides (especially cellulose derivatives such as benzylamino - methyl cellulose, acetyl - cellulose *p* - amino - benzoate, cellulose acetate diethyl aminoacetate), sugar derivatives such as sucrose *p* - amino - benzoate, mannitol *p* - amino - benzoate and dodecyl amine N - lactoside, and polyvinyl derivatives having basic amido groups (such as pyridine, piperidine or *tert* - amino groups) as well as mixtures of such polymers, (such as polyvinyl pyridine, polyvinyl piperidyl acetacetal, co-polymers of vinyl pyridine and styrene, and vinyl - diethylamine/vinyl - acetate co-polymers).

The manner in which the coating compositions of this invention are applied to conventional oral dosage forms of medicinals will be readily apparent to persons skilled in the art. In general, the coating operation is carried out using conventional methods and tech-

niques employing ordinary equipment. Usually the film-forming materials, that is the material which are resistant to gastric juices and those resistant to intestinal juices, are formed into a solution in some medicinally acceptable solvent. The film - forming materials, while contained in the solvent, are thereafter applied to the medicament. In forming the desired solution, one can employ any suitable pharmaceutically acceptable solvent in which the film-forming substance to be used is soluble. However, in the preferred embodiment of the invention, where cellulose acetate N,N - diethyl aminoacetate and cellulose acetate phthalate are employed as the coating materials, methylene chloride (or methylene chloride admixed with a relatively small quantity of a low molecular weight aliphatic alcohol) is used as the solvent. The concentration of the solution employed is variable within rather wide ranges. Completely satisfactory results will be obtained when the solution used contains from about 7 to 12 parts by weight of solvent for each part by weight of the film-forming material.

The actual coating operation is conventional. The uncoated medicament, in tablet form for example, is placed in a rotatable coating pan with the solution containing the coating substance resistant to intestinal juices. The pan is rotated to provide the tablets with a thin and uniform coat. The coated tablets are subsequently dried and the operation is repeated until the deposition of a thin layer of the coating substance on each tablet is assured. The insulating layer of hydrophilic substance is then applied to the tablets by the same technique, following which the tablets are rotated in the coating pan in a solution containing the substance resistant to gastric juice. Finally the external sealing coat is applied by usual methods.

Insofar as the medicament is concerned the present invention has wide applicability. In general, a pharmaceutical preparation containing any drug or combination of drugs can be coated in the manner described herein. The invention is, however, particularly well-suited for use in the coating of tablets and dragees containing emetine or dehydro-emetine as the active ingredient. Compositions containing emetine and dehydro - emetine are used for and are useful in the treatment of the two intestinal infections, amoebiasis and schistosomiasis. Prior to the present invention, the outstanding activity of these compounds was in part negatived by the fact that their oral tolerance was extremely poor. Even when these compounds were formulated into preparations which were resistant to gastric juices, their administration in very many instances resulted in the undesirable side effects of nausea, vomiting, abdominal pains and diarrhoea. It has been found that these side effects can be eliminated, or at the very least substantially reduced, when preparations containing emetine or dehydro - emetine are coated in a manner described herein. Emetine and dehydro - emetine can be used in their complexes with bismuth iodide.

Further examples of substances which can be used as the medicament in the practice of the present invention are: antimony potassium tartrate, acetyl - salicylic acid, sodium or calcium acetyl - salicylate, sodium salicylate, *p*-amino - salicylic acid and sodium or calcium *p* - amino - salicylate.

In order that the invention may be more clearly understood and readily carried into effect, the following examples are given:

EXAMPLE 1.

In this example, 1,000 coated tablets containing emetine hydrochloride as the active ingredient were prepared.

The preparative method involved the first step of mixing 70.0 g of lactose with 25.0 g of emetine hydrochloride. This mixture was moistened and granulated with a paste consisting of 2.5 g of swollen maize starch and 17.5 g of water. Thereafter, there was added to and mixed in, such granulate, 0.5 g of magnesium stearate and 2 g of talc. Thereafter, the granulate was pressed into 1,000 biconvex nuclei having a diameter of 7 mm.

There was then prepared a solution containing 2.0 parts of cellulose acetate diethylamino - acetate, 1.0 part of methyl alcohol and 17 parts of methylene chloride. This solution was charged into a conventional rotatable tablet-coating pan containing the tablet nuclei described in the immediately preceding paragraph. A film-coat was applied to the nuclei by rotating the coating pan. Subsequently, the nuclei were dried. Thereafter, the coating and drying operation was repeated fourteen times. The nuclei thus obtained had been provided with a coating which was resistant both to alkali and intestinal juices. These nuclei were dried for a period of about 12 hours at a temperature of about 40°C.

Thereafter, there was prepared a syrup containing 15.0 parts of white gelatine, 291 parts of water, 564 parts of sugar and 130 parts of gum arabic mucilage. This syrup was introduced into the rotatable tablet-coating pan containing the coated nuclei described in the preceding paragraph. The nuclei in the rotating pan were coated with the syrup until the total weight thereof, after drying, was 130 g. The tablets were then held for a period of about 12 hours at a temperature of about 40°C.

Subsequently, a lacquer solution containing 1.5 parts of cellulose acetate phthalate, 0.75 parts of methyl alcohol and 12.75 parts of methylene chloride was prepared. This solution was applied to the coated nuclei (obtained as described in the preceding paragraphs) in fifteen separate applications, the

nuclei being dried in between each application. Such application was carried out using the rotating tablet-coating pan. Subsequently, the thus coated nuclei were dried for a period of about 12 hours at a temperature of about 40°C.

At the end of the drying period, there was applied to the coated nuclei, a coating comprising 15.0 parts of white gelatin, 291 parts of water, 564 parts of sugar and 130 parts of gum arabic mucilage until a total weight of 170 g was reached. Thereafter, an additional layer was applied to the nuclei using the same gelatin-sugar syrup described heretofore but which also contained a colouring material. This sugar solution was applied in the rotating tablet-coating pan until the total weight of the tablets was 200 g. The coated preparations thus obtained were polished by continuously rotating same in a coating - pan containing beeswax.

The coated compositions produced as described in the preceding paragraphs were tested to ascertain the manner in which and the rate at which the active drug component was released therefrom.

In the test method employed, the coated compositions were subjected for a period of about one hour (in a tablet disintegration tester such as described in U.S. Pharmacopeia XVI, page 934) to an artificial gastric juice (pH 1.3) at a temperature of 37°C. At the end of that period of time, approximately one-half of the volume of the artificial gastric juice was removed and replaced by the same volume of artificial intestinal juice having a pH of 7.5. The artificial gastric juice which was recovered in this step was analyzed to ascertain whether emetine had separated from the composition by diffusion.

The compositions were then subjected for a period of about one hour to the thus obtained mixture of artificial gastric juice and artificial intestinal juice (pH 3.5) at a temperature of about 37°C. At the end of the one-hour period, one-half of the volume of the artificial digestive juice was removed and analyzed for emetine. The removed portion of the digestive juice was replaced with the same volume of artificial inestinal juice. The compositions were moved about in this juice for a period of about one hour, following which one-half of the volume of the digestion juice (pH 6.3) was removed and replaced with the same volume of artificial intestinal juice. The compositions were agitated in this juice for an additional one-hour period, following which one-half of the volume of the artificial juice (pH 7.0) was removed and replaced by the same volume of artificial intestinal juice. The compositions were subsequently moved about, for additional one-hour periods of time, in the digestion juice, one half of the juice being removed and replaced by the same volume of artificial intestinal juice after each one-hour period until the pH value of the juice has reached 7.5.

The table which follows hereinafter depicts the rate at which the drug component (that is to say, emetine) was replaced *in vitro* from the composition.

hours	released emetine (content of medicament in the dragee = 100%)
3	17%
4	24%
5	34%
6	45%
7	54%
8	61%
9	74%

The foregoing demonstrates that the release of emetine from the coated composition commenced only after an elapsed time of about two hours and that, subsequently, the release of the active drug from the coated tablet increased linearly at a rate of about 10 per cent per hour.

EXAMPLE 2.

In this example, coated compositions were prepared in the manner described in Example 1 using, except for the drug, the same ingredients and the same quantities thereof as were used in Example 1. In producing the product of this Example, dehydro - emetine di-

hydrochloride was used as the drug component.

The release characteristics of the product of this Example were comparable to those of the product of Example 1.

It will be appreciated that the term 'polyelectrolyte' is used in the foregoing description and in the claims appended hereto to mean a polymer having an ionisable group in the basic monomer moiety or in a part thereof in the case of a copolymer.

WHAT WE CLAIM IS:—

1) A coated pharmaceutical composition, characterised in that it comprises: (1) a nucleus containing the active drug and conventional pharmaceutical adjuvants, coated in sequence with (2) a layer of an acid-soluble coating material which is resistant both to alkalis and intestinal juices, (3) a layer of a hydrophilic substance and (4) a layer of an alkali-soluble coating material which is resistent to acid and to gastric juices.

2) A composition as claimed in claim 1, characterised in that the nucleus is coated in sequence with (a) a layer of a basic amino-containing polyelectrolyte, (b) a layer of a hydrophilic substance and (c) a layer of a carboxyl-containing polyelectrolyte.

3) A composition as claimed in claim 1 or claim 2, wherein the nucleus contains emetine hydrochloride or dehydro - emetine dihydrochloride.

4) A composition as claimed in claim 1 or claim 2, wherein the nucleus contains antimony potassium tartrate, acetyl - salicylic acid, sodium or calcium acetyl - salicylate, sodium salicylate, *p* - amino - salicylic acid or sodium or calcium *p* - amino - salicylate.

5) A process for the preparation of the compositions claimed in claim 1, which process comprises applying in sequence to a nucleus containing the active drug and conventional pharmaceutical adjuvants (a) a layer of an acid - soluble coating material which is resistant both to alkalis and intestinal juices, (b) a layer of a hydrophilic substance and (c) a layer of an alkali - soluble coating material which is resistant to acid and to gastric juices.

6) A process in accordance with claim 5, wherein the nucleus is coated in sequence with (a) a layer of a basic amino - containing polyelectrolyte, (b) a layer of a hydrophilic substance and (c) a layer of a carboxyl - containing polyelectrolyte.

7) A process in accordance with claim 5 or claim 6, wherein the nucleus contains emetine hydrochloride or dehydro - emetine dihydrochloride.

8) A process in accordance with claim 5 or claim 6, wherein the nucleus contains antimony potassium tartrate, acetyl - salicylic acid, sodium or calcium acetyl - salicylate, sodium salicylate, *p* - amino - salicylic acid or sodium or calcium *p* - amino - salicylate.

9) A process for the preparation of the compositions claimed in claim 1, substantially as described with reference to the Examples.

10) Compositions as set forth in claim 1, when prepared by the process claimed in any one of claims 5 to 9 inclusive.

W. D. WHITAKER,
Patent Agent,
for F. Hoffmann-la Roche & Co.,
Aktiengesellschaft.

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